detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse rodent, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.

REMARKS

The CPA filing of January 30, 2002 was done without paying the filing fee because Applicants intended to submit a preliminary amendment with the response to missing parts. However, it appears that the CPA has been treated as if the filing fee had been paid, an office action has issued, mailed March 13, 2002. As discussed with the Examiner, the Examiner will treat the present submission as a preliminary amendment and vacate the pending office action.

One of the principal issues in prosecution of the parent case was whether the various expression levels recited in the claims of the parent case were inherent in transgenic mouse models discussed in the cited art. The Examiner took the view that the expression levels recited in the claims of the parent case would likely have existed in transgenic mouse models discussed in the cited art notwithstanding that such expression levels were not actually determined in the cited art.

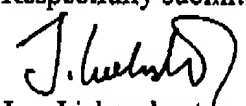
The claims pending in the present case moot this issue of inherency. The claims are directed to screening methods in which one starts with a plurality of transgenic mice, determines various expression levels of APP, APPα, APPβ, and /or Aβ as recited in the claims and then identifies a transgenic mouse having levels of these parameters satisfying certain threshold values recited in the claims, and uses a progency of such an mouse as a model of Alzheimer's disease. The levels of these parameters recited in the claims ensure that progeny of the transgenic mouse having the recited parameters develop useful pathological characteristics for drug screening assays. Because the cited art did not recognize the levels of the parameters

recited in the claims required to ensure suitable pathology, the cited art does not anticipate the present claims irrespective of the issues of inherency that were discussed in the parent case.

There are now two independent claims, claim 59 and 62, which are based on previous claims 1 and 33 respectively (although the reference to detection of Congo Red staining is not recited in claim 62). Claims 59 and 61 are both directed to methods of selecting a transgenic mice suitable for use as a model of Alzheimer's disease. Claims 60 and 62 add additional steps of screening the selected model mouse with an agent. The screening steps were previously recited in claims 1 and 33 respectively. Other dependent claims have been amended for conformity with the new independent claims. Support for the selection of a transgenic mouse from a plurality as recited in claims 59 and 61 can be found at *e.g.*, p. 47, lines 15-17 and the sentence bridging pp. 47-48. Support for using progeny of a selected transgenic mouse is provided at *e.g.*, p. 41, line 18.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 3 was amended as follows:

3. (Amended) The method of claim [2] 59 wherein the DNA encoding the Aβ-containing protein is cDNA or a cDNA/genomic DNA hybrid, wherein the cDNA/genomic DNA hybrid includes at least one APP intron sequence wherein the intron sequence is sufficient for splicing.

Claim 4 was amended as follows:

4. (Amended) The method of claim [1] 59 wherein the promoter is the human platelet derived growth factor β chain gene promoter.

Claim 5 was amended as follows:

5. (Amended) The method of claim [1] 59 wherein the region further comprises DNA encoding a second protein, wherein the DNA encoding the Aβ-containing protein and the DNA encoding the second protein are operative linked such that the region encodes an Aβ-containing fusion protein comprising a fusion of the Aβ-containing protein and the second protein.

Claim 7 was amended as follows:

7. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

Claim 9 was amended as follows:

9. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is a protein and the observed difference is a reduction or absence of the protein in plaques or neuritic tissue present in the transgenic mouse to which the compound has been administered.

Claim 11 was amended as follows:

11. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the enzymatic or biochemical activity of the protein in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

Claim 13 was amended as follows:

13. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is a nucleic acid encoding a protein and the observed difference is an increase or decrease in the amount of the nucleic acid present in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

Claim 15 was amended as follows:

15. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mouse to which the compound has been administered.

Claim 17 was amended as follows:

17. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or

severity of the histopathology present in the transgenic mouse to which the compound has been administered.

Claim 19 was amended as follows:

19. (Amended) The method of claim [1] 60 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mouse to which the compound has been administered.

Claim 20 was amended as follows:

20. (Amended) The method of claim [1] 60 wherein the marker is detected or measured using RT-PCR, RNase protection, Northern analysis, R-dot analysis, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron micrography.

Claim 22 was amended as follows:

22 (Amended) The method of claim [1] 60 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Trp, Met, Ser, Thr, Asn, and Gln.

Claim 24 was amended as follows:

24. (Amended) The method of claim [1] 60 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and/or

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Leu, Tyr, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

Claim 26 was amended as follows:

26. (Amended) The method of claim [1] 60 wherein the promoter mediates expression of the construct such that $A\beta_{tot}$ is expressed at a level of at least 30 nanograms per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, $A\beta_{1-42}$ is expressed at a level of at least 8.5 nanograms per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, APP and APPα combined are expressed at a level of at least 150 picomoles per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, and/or mRNA encoding the Aβ-containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mouse in hippocampal or cortical brain tissue of the mouse when it is two to four months old.

Claim 31 was amended as follows:

31. (Amended) The method of claim [1] 59 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding the Aβ-containing protein.

Claim 33 was canceled.

Claim 34 was amended as follows:

34. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

Claim 36 was amended as follows:

36. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is a protein and the observed difference is a reduction or absence of the protein in plaques or neuritic tissue present in the transgenic mouse to which the compound has been administered.

Claim 38 was amended as follows:

38. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the enzymatic or biochemical activity of the protein in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

Claim 40 was amended as follows:

40. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is a nucleic acid encoding a protein and the observed difference is an increase or decrease in the amount of the nucleic acid present in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

Claim 42 was amended as follows:

42. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mouse to which the compound has been administered.

Claim 44 was amended as follows:

44. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or

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severity of the histopathology present in the transgenic mouse to which the compound has been administered.

Claim 47 was amended as follows:

47. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mouse to which the compound has been administered.

Claim 48 was amended as follows:

48. (Amended) The method of claim [33] 62 wherein the marker is detected or measured using RT-PCR, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron micrography.

Claim 49 was amended as follows:

49. (Amended) The method of claim [33] 62 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Tip, Met, Ser, Thr, Asn, and Gln.

Claim 51 was amended as follows:

51. (Amended) The method of claim [33] 62 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

Claim 53 was amended as follows:

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53. (Amended) The method of claim [33] 62 wherein the Alzheimer's disease marker is selected from the group consisting of $A\beta_{tot}$, $A\beta_{1-42}$, $A\beta_{N3}(pE)$, $A\beta_{x-42}$, and $A\beta_{Insoluble}$.

Claim 54 was amended as follows:

54. (Amended) The method of claim [33] 62 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding a human amyloid precursor protein.

Claim 57 was amended as follows:

57. (Amended) The method of claim [1] 59 wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717.

Claim 58 was amended as follows:

58. (Amended) The method of claim [33] 61 wherein the region of the construct encoding a human amyloid precursor protein is selected from the group consisting of APP770 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP751 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; the APP695 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations;

APP695, APP751, or APP770 cDNA truncated at amino acid 671 or 685; APP cDNA truncated to encode amino acids 646 to 770 of APP; a combination cDNA/genomic APP gene construct bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; and a combination cDNA/genomic APP gene construct truncated at amino acid 671 or 685.

The following new claims were added.

59. A method of selecting a transgenic mouse as a model of Alzheimer's disease, comprising

providing a plurality of transgenic mice, each comprising a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell and a region encoding an Aβ-containing protein, wherein the promoter is operatively linked to the region,

wherein the region comprises DNA encoding the Aβ-containing protein, wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717; a protein consisting of amino acids 672 to 770 of APP; and a protein consisting of aminoacids 672 to 714 of APP;

determining expression levels of APP, APPβ and APPα and Aβ in each of the transgenic mice;

identifying a transgenic mouse wherein Aβtot is expressed at a level of at least 30 nanograms per gram of brain tissue of the mouse when it is two to four months old, Aβ1-42 is expressed at a level of at least 8.5 nanograms per gram of brain tissue of

the mouse when it is two to four months old, APP and APP combined are expressed at a level of at least 150 picomoles per gram of brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of brain tissue of the mouse when it is two to four months old, and mRNA encoding the Aβ-containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mouse in brain tissue of the mouse when it is two to four months old;

using an offspring of the identified transgenic mouse as a model of Alzheimer's disease.

60. The method of claim 59, further comprising administering a compound to be tested to the offspring or cells derived therefrom, and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse rodent, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.

61. The method of claim 59, wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717.

62. A method of selecting a transgenic mouse as a model of Alzheimer's disease, comprising

providing a plurality of transgenic mice, each comprising a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell and a region encoding an Aβ-containing protein, wherein the promoter is operatively linked to the region,

wherein the region comprises DNA encoding the Aβ-containing protein, wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, a protein consisting of amino acids 672 to 770 of APP; and a protein consisting of amino acids 672 to 714 of APP;

determining expression levels of Aβ and Congo red staining in the brains of each of the transgenic mice;

identifying a transgenic mouse;

wherein Aβ is expressed at a level of at least 50 ng/g brain tissue in the identified transgenic mouse when the transgenic mouse is three months of age; and

using an offspring of the identical transgenic mouse as a model of Alzheimer's Disease.

63. The method of claim 62, further comprising administering a compound to be tested to the offspring or cells derived therefrom, and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse rodent, and the marker in a transgenic mouse to which the compound

has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.